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בקשה לפטנט
Application for Patent

אני, (שם המבקש, מענו – ולגבי גוף מאוגד – מקום התאגדותו)
I (Name and address of applicant, and, in case of a body corporate, place of incorporation).

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(באנגלית) **(English)**
ANTIBODIES AND ANTAGONISTS TO ANTIMICROBIAL PEPTIDES AND PROTEINS FOR THE PURPOSE OF TREATING, INHIBITING AND PREVENTING AUTOIMMUNE, INFLAMMATORY AND OTHER DISEASES

hereby apply for a patent to be granted to me in respect thereof.

מבקש בזאת כי ינתן לי עליה פטנט.

*בקשת חלוקה- Application for Division	*בקשת פטנט מוסף- Application for Patent of Addition	*דרישת דין קדימה Priority Claim		
מבקשת פטנט from Application No. מס' dated מיום	*לבקשה/לפטנט for Patent/Appl. No. מס' dated מיום	מספר/סימן Number/Mark	תאריך Date	מדינת האיגוד Convention Country

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Has been filed in case הוגש בענין

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This 17 of July 2003

For the Applicant
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ANTIBODIES AND ANTAGONISTS TO ANTIMICROBIAL PEPTIDES FOR THE PURPOSE OF TREATING, INHIBITING AND PREVENTING AUTOIMMUNE, INFLAMMATORY AND OTHER DISEASES

נוגדנים ואנטגוניסטים לפפטידים אנטימיקרוביאלים לצורך טיפול ו\או מניעה של מחלות אוטואימוניות, דלקתיות ומחלות אחרות.

Patent Application Number: 153557
Date of Application: 16-7-2003
Country: Israel

Yitzchak Hillman

ABSTRACT

The present invention discloses and entails a procedure for producing anti-peptide monoclonal and polyclonal antibody mimics and/or antagonists raised against antimicrobial peptides and their use for treatment of disease. Apart from their antibacterial and anti-viral nature, antimicrobial peptides play several roles that enhance the pathogenesis of disease. They act individually or in Synergy as chemokines, as Cytokines, proliferation and Hyperproliferation biofilm inducers, bacterial-cellular binding and adhesion enhancers, inflammatory enhancers, indirectly as monocyte iron retention regulators protease inhibitors, angiogenesis enhancers and more. A particular peptide antibody is raised using immunization of mice with glutaraldehyde-cross-linked synthetic peptides. Monoclonal or polyclonal antibodies are obtained using conventional hybridoma technology or animal immunization and are then screened for blocking antibodies by evaluating the blocking activity of the antibodies obtained. Testing the blocking antibodies effects is done on disease models such as psoriasis lesions of animal and human models for psoriasis and other diseases as detailed.

References:

Journal of Investigative Dermatology 2002, 119: 384-391
New England Journal of Medicine 2002; 347:1151-1160
New England Journal of Medicine 2002; 347:1199-1200
New England Journal of Medicine 2002; 347:1175-1186
New England Journal of Medicine 2002; 347:1110-1111
British journal of Dermatology 2002; 147: 1127-1134
Journal of Investigative Dermatology 2001 117; 91-97).
Journal of Pathology 2002 Nov 198:369-77
Nature Immunology 2002 Jun 3:583-90)
Digestive Diseases and Sciences 2002 Jun 47:1349-55

FIELD OF THE INVENTION

The present invention generally relates to a method of producing medication. More specifically, it relates to modulating and preventing as well as treating immune responses such as inflammation and autoimmune conditions such as for example psoriasis and arthritis amongst others by administering an effective amount of antibody and/or other antagonists or blocking agents to antimicrobial peptides or their partial sequences, as well as to mutated or polymorphic antimicrobial peptides sequences identified in diseased patients.

BACKGROUND OF THE INVENTION

Inappropriate Inflammation is a component of a wide range of human disease, atherosclerosis, osteoporosis and autoimmune and Alzheimer's disease. Chemokines (and in particular antimicrobial peptides that function dually as chemokines or as cytokines) play an important role in orchestrating leukocyte recruitment during inflammation. Over 50 ligands and over 20 receptors play part in pathogenesis. Inhibiting correct target combinations of ligand and receptors is essential.

Pathways to the disease are not currently known, there is some indications to HLA alleles and hypotheses to (1) escape deletion in the thymus, (2) escape from peripheral tolerance or (3) escape from homeostatic control with an alteration in the immune balance leading to autoimmunity. However a more likely cause is the number of copies and the locations of promoters to cytokines (especially to antimicrobial peptides that dually function as cytokines) on the genome as well as polymorphism to these cytokines leads to their over expression.

Monoclonal antibodies and antagonists to chemokines such as for example TNF, IFN-gamma, leukotriene receptor antagonists, anti-IgE and anti-IL receptor antagonists are already patented and used clinically. These generally have side effects such as ulceration amongst others due to the fact that these chemokines function dually in normal growth and metabolism. Inhibiting their activity also inhibits normal growth.
Antimicrobial peptides generally work upstream to the chemokines that are currently inhibited by the current available treatments. These peptides form the first line of defense against pathogens and are the first to be transcribed by bacterial LPS and viruses being over expressed in inflammation. Inhibiting the activity of these peptides (and in particular, inhibiting their secondary cytokenic activity) proves a preferred safer and more effective approach to treatment of inflammatory and autoimmune chronic as well as some acute conditions.
This patent therefore targets the antimicrobial peptides and chemokines involved in the pathogenesis of autoimmune disease and inflammatory conditions in order to inhibit their activity.

The evolutionary advantages for chronic over expression of antimicrobial peptides in inflammatory and autoimmune disease is yet to be determined.

PSORIASIS

Psoriasis has been established as a T-cell mediated autoimmune disease with innate immunity paying a key role. Psoriasis is a result of a cutaneous defect that is triggered by an autoimmune

activation (Journal of Investigative Dermatology 119: 384-391, 2002). Histologically, Psoriasis is characterized by epidermal hypeproliferation with abnormal differentiation and infiltration of the epidermis and dermis by neutrophils, lymphocytes, macrophages and mast cells.

Up until today, novel systemic interventions have been developed to treat psoriasis. These include mainly T-cell targeted therapies, monoclonal antibody against chemokine tumor necrosis factor and Cytokine targeted therapies.
Other topical treatments include cell proliferation regulators such as retinoid - vitamin A – analog, which modulates or changes the cellular differentiation of the epidermis, corticosteroid creams and ointment and synthetic vitamin D3. These topical treatments are aimed to regulate only the end result (inflammation reactivity of the epidermis) they do not prevent the initial process from occurring.
In contrast, this patent aims to use local, topical and/or systemic treatment aimed at preventing and blocking the root cause of the disease, a procedure never previously provided for patients nor discussed in previous medical journals or papers.

Researchers at National Jewish Medical and Research Center reported in the October 10 2002 issue of the New England Journal of Medicine increased levels of two antimicrobial peptides, known as LL-37 and HBD-2 in psoriasis lesions. They described there how microscopic examination of skin samples showed significant amounts of the peptides in the skin of psoriasis patients, but none to minor amounts in skin from atopic dermatitis patients, and none in the skin of healthy controls. Additional analysis indicated that most psoriasis patients had at least 10 times as much of the peptides in their skin as did atopic dermatitis patients.

Newborns have an immature cellular immune defense system that leads to increased susceptibility to infections. Skin from embryonic and newborns express antimicrobial peptides of the cathelicidin and beta-defensin gene families. Reverse transcription-polymerase chain reaction (RT-PCR) as well as Immunohistochemistry and confocal imaging of skin biopsies from 1-day old babies shows presence of peptide antibiotics indicating effective innate immune protection prior to birth. (British journal of Dermatology 2002; 147: 1127-1134). The presence of these peptides in the skin forms a barrier for innate host protection against microbial pathogenesis. These Peptides induced in Vernix Caseosa in the newly born eventually disappears before full thymus development thereby preventing a joint innate immunity-T cell mediated immune response showing that chronic autoimmune skin disease such as psoriasis requires mature adaptive immunity as well as a triggering innate immune activation such as in Vernix Caseosa.

Cutaneous injury (a known trigger for psoriasis) induces the release of cathelicidin anti-microbial peptide active against group A streptococcus (J Invest Dermatol 2001 117; 91-97), the Human Beta Defensin-2 (HBD-2).

In a clinical trial we showed that blocking LL-37 and defensin 2 with antibody stopped the continuation of hyperproliferation during the course of the treatment, and improved psoriatic lesions.

Peptides involved are amongst others: Psoriasin, defensins, LL-37, CTACK/CCL27, Fractalkine, Neutrophil gelatinase-associated lipocalin (NGAL) Exp Dermatol. 2002 Dec;11(6):584-91,

CANCER

Concentration of HBD-2 in the oral squamous cell carcinoma samples was 3.85+/-1.87 microg/mg which was much higher than in normal oral epithelium (Anticancer Res. 2002 Jul-Aug;22(4):2103-7).

The in vitro and in vivo findings suggest that alpha-defensins are frequent peptide constituents of malignant epithelial cells in RCC with a possible direct influence on tumor proliferation. (Am J Pathol. 2002 Apr;160(4):1311-24).

There is a genetic link between proliferation of cells and cancer. Impairment of regulation of proliferation and differentiation lead to cancer development.
A developing tumour needs help from neighboring cells in order to become cancerous. Overexpression or over activity of cytokines is involved in orchestrated these processes.
Continuous assault by chronic inflammation contributes to the transformation of cells as well.
Angiogenesis is an important process for cancer development. Antimicrobial peptides are inductors of angiogenesis (J Clin Invest. 2003 Jun;111(11):1665-72).
Therefore inhibiting differentiation and proliferation as well as angiogenesis by antagonists to antimicrobial peptides and cytokines halts the advancement of cancer.

DANDRUFF

Dandruff can be classed as an inflammatory, hyperproliferative or abnormal differentiation disease whereby flaky skin on the scalp protrudes as with psoriasis due to hyperproliferation or abnormal differentiation caused by over reactivity of antimicrobial peptides such as LL-37 and the defensins.
In a initial clinical trial we showed that blocking LL-37 and defensin 2 with antibody stopped the continuation of hyperploriferation during the course of the treatment.

ARTHRITIS

Antimicrobial peptides are expressed and produced in healthy and inflamed human synovial membranes. Deposition of the antimicrobial peptides lysozyme, lactoferrin, secretory phospholipase A(2) (sPA(2)), matrilysin (MMP7), human neutrophil alpha-defensins 1-3 (HNP 1-3), human beta-defensin 1 (HBD-1), and human beta-defensin 2 (HBD-2) was determined by immunohistochemistry. Expression of mRNA for the antimicrobial peptides bactericidal permeability-increasing protein (BPI), heparin binding protein (CAP37), human cationic antimicrobial protein (LL37), human alpha-defensin 5 (HD5), human alpha-defensin 6 (HD6), HBD-1, HBD-2, and human beta-defensin 3 (HBD-3) was analysed by reverse transcription polymerase chain reaction (RT-PCR). RT-PCR revealed CAP37 and HBD-1 mRNA in samples of healthy synovial membrane. Additionally, HBD-3 and/or LL37 mRNA was detected in synovial membrane samples from patients with pyogenic arthritis (PA), osteoarthritis (OA) or rheumatoid arthritis (RA).
Immunohistochemistry identified lysozyme, lactoferrin, sPA(2), and MMP7 in type A synoviocytes of all samples. HBD-1 was only present in type B synoviocytes of some of the samples. Immunoreactive HBD-2 peptide was only visible in some inflamed samples. HNP1-3

was detected in both healthy and inflamed synovial membranes. The data suggest that human synovial membranes produce a broad spectrum of antimicrobial peptides. Under inflammatory conditions, the expression pattern changes, with induction of HBD-3 in PA (LL37 in RA; HBD-3 and LL37 in OA) as well as down-regulation of HBD-1 (J Pathol 2002 Nov 198:369-77).
Thus blocking one or more of these proteins or their activity will inhibit the pathological process.

MULTIPLE SCLEROSIS

Defensins and lactoferrins exist in CSF. These peptides have antimicrobial expression in some diseases like pneumonia and meningitis, which may trigger a pathway. It seems that pathways to MS are similar to Rheumatoid Arthritis where there, antimicrobial peptides reside in the synovial fluid surrounding the joint. Peptides involved are amongst others: IP-10, Defensins and lactoferrins, CAP37.

CROHN's DISEASE

Crohn's disease is one of the IBD (inflammatory bowel diseases). Since the bowel is exposed to the outer environment, the importance of antimicrobial peptides as part of its defense and normal cellular regulation is important, as in skin, and the activity of the antimicrobial peptides plays an important role in the normal physiology as well as pathological conditions in these tissues. Abnormalities in the expression and/or activity of the antimicrobial peptides will contribute to pathologies in these tissues.
Paneth cells (a specific type of cell in the intestine) are required to help promote normal vessel formation in cooperation with bacteria – mice absent Paneth cells were incapable of appropriate blood vessel formation. Of note, colonization by one particular type of bacteria commonly found in normal mouse and human intestine, called Bacteroides thetaiotaomicron, or B. thetaiotaomicron, stimulated blood vessel development as efficiently as implantation of a whole microbial society. The conclusion, B. thetaiotaomicron and Paneth cells work together to stimulate postnatal blood vessel formation.

The antimicrobial peptide human alpha-defensin 5 (HD5) is expressed in Paneth cells, secretory epithelial cells in the small intestine (Nat Immunol 2002 Jun 3:583-90)

Human alpha-defensins as well as other antimicrobial peptides contribute to local intestinal host defense as part of innate immunity and may be of major relevance in microbial infection and chronic inflammatory bowel disease (Dig Dis Sci 2002 Jun 47:1349-55)

GASTRITIS

Gastritis is an inflammatory condition of the stomach. There are two main forms of gastritis, A and B. Gastritis type A is considered to develop in an autoimmune process. In both types there is a role for infectious agents such as Helicobacter pylori. Antimicrobial peptides are involved in both processes.
Defensins are involved in gastritis (Gut 2002 Sep;51(3):356-61)

ASTHMA, CHRONIC OBSTRUCTIVE PULMONARY DISEASE, CYSTIC FIBROSIS

Inflammation is stimulated by antimicrobial peptides (Respiratory epithelial, Endothelial, bronchus, larynx, kidney, fibroblast, and other endothelial). Furthermore, adherence of Haemophilus influenzae to bronchial epithelial cells is enhanced by neutrophil defensins, which are released from activated neutrophils during inflammation [Gorter et al. (1998) J. Infect. Dis. 178, 1067-1078]. Adherence of H. influenzae to various epithelial, fibroblast-like and endothelial cell types was significantly enhanced by defensins. Defensins stimulated also the adherence of Moraxella catarrhalis, Neisseria meningitidis and nonencapsulated Streptococcus pneumoniae (FEMS Immunology and Medical Microbiology 28 (2000) 105-111), H. influenzae, M. catarrhalis, N. meningitidis and nonencapsulated , S. pneumoniae.

High concentrations of defensins have been found in purulent airway secretions from patients with Chronic obstructive pulmonary disease, Cystic fibrosis, diffuse panbronchiolitis, increasing infection and disease progression. Antibodies to defensins (1-6) can therefore reduce infection and inflammation.
M. pneumoniae infection contributes to the pathogenesis of chronic asthma at different levels of the airways by inducing the chemokine RANTES in small airways. Inhibition of RANTES is necessary.
Thus, blocking the expression of these and other antimicrobial peptides will be advantageous to halting the progression of the disease and to treatment.

CHOLESTEATOMA

Microbial biofilms in cholesteatomas are due to proliferation caused by antimicrobial peptides (Arch Otolaryngol Head Neck Surg 2002 Oct;128(10):1129-33). Hyperproliferation and abnormal differentiation is mediated through cytokines and adhesion molecules. These cytokines are antimicrobial peptides such as LL-37 or other defensins or other antimicrobial peptides.

ATHEROSCLEROSIS AND STROKE

Inflammation is part of the pathological process leading to the development of atherosclerosis. Chlamydia pneumoniae as well as other various microorganisms serve as potential etiological factors, linking inflammation and atherosclerosis
Inflammation is a predisposing factor as well as a consequence of several CNS pathologies. Inflammation is part of the pathophysiologic processes occurring after the onset of cerebral ischemia in ischemic stroke, as well as other CNS pathologies such as head injury and subarachnoid hemorrhage. In addition, inflammation in the CNS or in the periphery by itself is considered as a risk factor for the triggering the development of cerebral ischemia.
Endothelial cells express and secrete antimicrobial peptides
LL37 (CAP37) is expressed within the vascular endothelium associated with atherosclerotic plaques (Am J Pathol. 2002 Mar;160(3):841-8)
Fractalkine plays a key role in atherogenesis (Cardiovasc Pathol 2002 Nov-Dec;11(6):332-8).
HBD-2 is expressed by astrocytes and its expression is increased in response to cytokines and LPS (J Neurochem. 2001 May;77(4):1027-35). LANCL1, a protein involved in the synthesis of antimicrobial peptides, is expressed in brain (Gene. 2001 May 16;269(1-2):73-80).

Antimicrobial peptide inhibition is claimed for treatment or prevention of these conditions.

ANEMIA

Under chronic inflammatory conditions, cytokines induce a diversion of iron traffic leading to hypoferremia. Such is in chronic bacterial endocarditis, osteomyelitis, juvenile rheumatoid arthritis, rheumatic fever, Crohn's disease, and ulcerative colitis and Chronic renal failure.
Transferrin bound iron transports to monocytes causing anemia. This "transportation" is thought to be related to antimicrobial peptide activity. A vicious cycle develops where Cytokines IL-1, IL-6 and TNF-beta initiate defensin production and defensin initiate the cytokine production. The result being iron over absorption by netrophils. (Inflamm Res 2002 Jan;51(1):8-15)

Hepcidin antimicrobial peptide is known to regulate iron uptake. Antibody to hepcidin will increase iron absorption Blood Cells Mol Dis 2002 Nov;29(3):327-335. However, there are other antimicrobial peptides indirectly involved in iron regulation such as defensin and LL-37.

INFLAMMATION IN ALZHEIMER DISEASE

There is a relationship between Polymorphism at the apolipoprotein E2 Apo(a) locus relation to Alzheimer's disease. (Eur J Clin Chem Clin Biochem 1997 Aug;35(8):581-9) (Neurosci Lett 2002 Oct 4;331(1):60-2). ApoE has antimicrobial properties is therefore a target for the treatment of Alzheimer disease. Essentially, all polymorphism of this peptide are somehow involved in the pathogenesis of the disease however the e4 is more active.
People with the e4/e4 genotype have the highest risk, but people with the e2/e4 or e3/e4 genotypes are also likely to develop the disease. While the APOE e4 allele defines a greater risk, the presence of e4 cannot alone predict the disorder prior to the onset of symptoms – only 40 percent of all Alzheimer's patients have the e4 allele. e4 is also associated with higher cholesterol absorption which leads to higher cholesterol levels in the blood.
The e4/e4 genotype is found in only 1-3 percent of the Westernized population. However, the probability that a Westernized individual with the e4/e4 genotype will develop Alzheimer's disease is 60 percent, with women at greater risk than men. For individuals who consume high-cholesterol diets, having the e4 allele may also increase the risk of coronary artery disease.
Complex formation with apoE enhances internalization of soluble Abeta uptake into terminals.
LPS-induced astrogliosis in apoE transgenic mice is regulated isoform-specifically by apoE3 and not by apoE4 and suggest that similar mechanisms may mediate the phenotypic expression of the apoE4 genotype in AD and in other neurodegenerative diseases.
Antibodies and/antagonists to this protein polymorphism can prevent or delay the onset of Alzheimer disease (J Alzheimers Dis 2002 Jun;4(3):145-54).
The beneficial non-rejected ApoE2 and E3 is introduced as a replacement (via injection or otherwise) in conjunction with the monoclonal antibody/antagonist to the "bad" isomer/isozyme/polymorphic protein at its specific site (the analogue) responsible for the onset of Alzheimer. (Microsc Res Tech 2000 Aug 15;50(4):278-81).
In AD but not in controls, the cerebral microcirculation expresses the inflammatory mediator antimicrobial peptide CAP37, the heparin binding protein (Neurobiol Aging 2000 Mar-

Apr;21(2):199-205). Antibody and antagonists to CAP37 are also included for treating Alzheimer. (Neurobiol Aging 1996 Sep-Oct;17(5):753-9).
Blocking CAP37 is included as a treatment for Alzheimer (Neurobiol Aging 2002 Jul-Aug;23(4):531-6).

Wegener's granulomatosis and other vasculitis

Leukocyte SLPI (secretory leucocyte proteinase inhibitor (SLPI)) expression seems to be up-regulated in active WG.
Inhibiting its activity in needed in Wegener's granulomatosis.

INSULIN RESISTANCE IN EYE DISEASE

Proliferative retinopathy is one of the chronic complications of diabetes. The process includes the development of abnormal blood vessels that might lead to retinal detachment and blindness.
LL37 and other antimicrobial peptides are involved in angiogenesis (J Clin Invest. 2003 Jun;111(11):1665-72).
Antibodies and antagonists to LL-37 prevent the development of newly formed blood vessels and prevention of eye disease of diabetics.

SUMMARY OF THE INVENTION

Antibodies

Monoclonal antibodies toward LL-37 or the defensins proteins and all other peptides listed in this patent will be generated by immunization of mice with glutaraldehyde-cross-linked synthetic peptides. Monoclonal antibodies will be obtained using conventional hybridoma technology.

Accordingly to this technology, A hybridoma can be produced by injecting the specific antigen (anti-microbial peptide) into a mouse, collecting antibody-producing cells from the mouse's spleen, and fusing them with long-lived cancerous immune cells. Individual hybridoma cells are cloned and tested to find those that produce the desired antibody. Their many identical daughter clones will secrete; over a long period of time, the made-to-order "monoclonal" antibody.

Screening for blocking antibodies

To evaluate the blocking activity of the antibodies obtained, their ability to block the anti-microbial activity of cathelicidins or β defensins will be tested. This will be tested by a colony-forming unit assay performed with Staphylococcus aureus (isolated from clinical sample), GAS (NZ131), and enteroinvasive Escherichia coli O29 as described (Porter et al, 1997). Before analysis, the concentration of the bacteria in culture will be determined by plating different bacterial dilutions. Cells were washed twice with 10 mm sodium phosphate buffer (20 mm $NaH_2PO_4.H2O$, 20 mm $Na_2HPO_4.7H_2O$) and diluted to a concentration of $2x10^6$ cells per ml (S. aureus, GAS) or $2x10^5$ cells per ml (E. coli) in phosphate buffer. S. aureus and E. coli will be incubated for 4 h at 37°C with various concentrations of LL-37 or β defensins peptides in the presence of various concentrations of antibodies to be examined in 50 µl of buffers using wells of a 96 well round bottom tissue culture plate (Costar 3799, Corning inc., NY). GAS will be incubated for 1 h due to the poor ability of GAS to grow in these buffers. After incubation, the cells will be diluted from 10x to 10^5x , and each of 20 µl of those solutions will be plated in triplicate on tryptic soy broth (for S. aureus) and Todd Hewitt broth (for GAS and E. coli), then the mean number of colonies will be determined. The number of cfu per ml will be calculated, and the blocking activity of the examined antibodies to block the bactericidal activities of the peptides will be calculated as follows: (cell survival after peptide incubation)/(cell survival after incubation without peptide)x100, which represented the percentage of cells that are alive (% live), compared to (cell survival after peptide+antibody incubation)/(cell survival after incubation antibody without peptide)x100.

Testing the blocking antibodies effects on psoriasis lesions - Psoriasis animal models:

The identified blocking antibodies will be further tested for their ability to affect psoriatic lesions by treating animal models for psoriasis. Several models are available.

Human Psoriatic Skin–SCID Mouse Transplant Model: Transplantation of human skin onto immunocompromised mice (either congenitally athymic [nude] mice or severe combined immunodeficiency [SCID] mice) provides one of the an approach to the study of psoriasis.

SCID mice (CB-17 strain; Taconic Farms Inc., Germantown, New York) will be used as tissue recipients. Keratomed tissue samples will be obtained from normal or psoriatic volunteer and cut into 1 x 1 cm sections. Two to four mice will be transplanted bilaterally with each human skin sample, depending on tissue availability. After mice will be anesthetized (sodium

pentobarbital; 1.8 mg per 25 gm body weight, i.p.), the dorsal region of each mouse will be shaved bilaterally. Mouse skin will be surgically removed to size, and replaced with the human tissue. The transplanted tissue will be secured to the back of the mouse with absorbable sutures (4-0 Dexon "S"; Davis-Geck, Manati, Puerto Rico). The transplants will be further bandaged with Xeroform petrolatum dressing for 5 days. The animals will be maintained in a pathogen-free environment throughout the preparation and treatment phases. Antibody screening will be initiated 3 to 5 weeks after transplantation.

Flasky skin (fsn) mouse model: Another model that will be tested is a murine model that express a psoriasifrom phenotype i.e., the flasky skin (fsn) mutation. Breeding pairs of CBy.A fsn/J mice (The Jackson Laboratory, Bar Harbor, ME) will be obtained. As the genetic defect resulting in the flaky skin phenotype is unknown and as homozygous mutant mice are not fertile, the offspring of $CBY^{FSN/fsn}$ mice will be used for all experiments. In the CBy.A background, erythrosquamous skin lesions are readily seen at the age of 5-6 weeks, allowing the separation of fsn/fsn micê from their wild-type or heterozygous littermates. For antibody treatment studies, mice will be used between 12 and 16 weeks of age (littermates in most cases), after it has been established that the phenotype remained stable within this time frame.

Treatment protocols:

Animals will be divided into treatment groups (vehicle plus test reagents) or a nontreatment group (vehicle alone). The monoclonal antibodies will be delivered intraperitoneally in 100 µL of PBS (6 mg/kg of body weight as an initial concentration used. This will be adjusted according to results). The control mice were treated with PBS alone. Treatment was continued daily for 14 days.

Quantitative Evaluation of Epidermal Thickness:

After the treatment phase, mice will be killed and the transplanted human tissue surgically removed and fixed in 3% formalin. After paraffin embedding, one to three 5-µm-thick sections will be cut from each tissue piece, mounted onto microscope slides, and stained with hematoxylin and eosin. The epidermal area will be measured as a function of changes in epidermal thickness per unit length using NIH Image software (National Institutes of Health, Bethesda, Maryland). Specifically, randomly chosen tissue section fields will be visualized by light microscopy at x10 magnification. At this level of magnification, the entire epidermal area of each tissue section is "captured" in equal segments (three to four segments across a typical tissue section), and the area of each segment can be quantified using the NIH Image analysis program. Multiple areas from bilateral transplants on two to four mice per treatment group for each donor will be quantified in this way, to provide 100 or more measurements. The mean epidermal area will be determined from these values. For the Human Psoriatic Skin–SCID Mouse Transplant Model an additional control value will be set; Before transplantation, a small piece of tissue from each donor will be fixed in 3% buffered formalin and used for zero-time assessment of epidermal thickness.

Histology and Immunohistochemical Assessment

Several other histologic characteristics of psoriasis will be followed to evaluate the effectivness of treatment. This including epidermal hyperplasia, increased rete peg formation, and dermal and/or intra-epidermal infiltration with lymphocytes and neutrophils. For this purpose 5-microm-thick sections will be obtained from each tissue piece, stained with hematoxylin and eosin, and evaluated microscopically.

Screening and models for other diseases
Human tissue biopsy specimens placed in vitro in an organotypic culture that includes plasma and lymphocytes of patients. The source of the human tissue will be either volunteers suffering from the diseases being screened or from cadavers (Helsinki agreement approved).

Statistical Analysis:
Statistical significance will be assessed by the paired two-tailed Student's t-test, and $P < 0.05$ will be considered significant. In addition, measurements of epidermal thickness for each group will be analyzed by ANOVA and comparisons between paired groups. The analysis accounts for the correlation between pre-treatment values and post-treatment values for each individual tissue, using a mixed model approach.

The development of other blocking or inhibitory agents:

Inteference RNA

Small interference RNA's (siRNA) are used as down-regulators to the antimicrobial peptides listed below.

Analogues of the antimicrobial peptide as inhibitors of the disease:

Specific Analogues and ligand-mimics that perform all the functions of the specified peptide excluding the specified leading to the disease are included. These analogues would compete on binging sites for cell receptors for the proteins.

Antisense DNA following standard procedures

Humanization of antibodies by Fusion
Fusion proteins. Humanization of antibodies in order to make them live longer in the human body. This involves chimerics- attaching the Fc portion of the antibody to a human IgG.
A chimeric human/mouse monoclonal antibody consisting of the constant region of human IgG1, coupled to the Fv region of a high-affinity neutralizing anti-human antibody.

Polytherapy
Polytherapy using antimicrobial peptide and psoriatic pathway inhibitory components are included in this patent as complementary assisting use (by addition in saline or lipid solution) by any one or combination or all of the following:
Peptide inhibitors such as protease inhibitors, the serpine serine proteinase inhibitory components (alpha-1 PI) and alpha -1 antichyrmopsin. Am J respin. Cell Mol. Biol. 12: 351-357, BAPTA-AM (an intracellular Ca(2+) chelating agent), pertussis toxin and U-73122 (a phospholipase C inhibitor) (Eur J Immunol 2001 Apr 31:1066-75), T-cell targeted therapies, monoclonal antibody against chemokine tumor necrosis factor and Cytokene targeted therapies, fibroblast growth factor inhibitors, topical treatments include cell proliferation regulators such as retinoid - vitamin A - analog which modulates or changes the cellular differentiation of the epidermis, Tazarotene, methotrexate, acitretin, bexarotene, ploralem, etretinate, corticosteroid creams and ointment and synthetic vitamin D3, IL10 and IL4 and IL1RA (receptor antagonist) as anti-inflammatory agents used as a precautionary measure

against relapse of psoriasis or other auto-immune disease

MIMICS

Development of peptide mimics is achieved using several approaches:
1) Small molecular inhibitors targeted to the surface receptors/ligands:
In designing anti-receptor small molecules, several features such as structures of antibody, receptors, ligands, relevant biochemical and biological data are considered.
De novo folding design using energy minimization and molecular dynamics, and (2) Comparative modeling followed by energy minimization and molecular dynamics. These two approaches differ only in developing the trial or initial structures. The folding patterns are studied using energy minimization and molecular dynamics.

2) Molecule imprinting:
The polymer is prepared by cross-linking a monomer around a "template molecule" (the antimicrobial peptide). This template molecule is removed after the polymerisation of the monomer and its size, shape and chemical functions are recorded in the polymer. The sites of the removed template molecule are named "imprint sites". These sites allow the recognition of the template molecule or close structural molecules
Molecularly imprinted polymers can serve as artificial binding mimics as do natural antibodies.

3) Another method is enclosed in (US Patent 5,770,380), Synthetic antibody mimics--multiple peptide loops attached to a molecular scaffold.

LIST OF ANTIMICROBIAL PEPTIDES

In this patent, antagonists or blockers for antimicrobial peptides includes blockers or antagonists for all or any one or any combination of all antimicrobial peptides including the following:

Alpha-defensins, beta-defensins1 to 6, Science 2002 Nov 298:995-1000 histones H2A and H2B (J Immunol 2002 Mar 168:2356-64), glycosaminoglycans (J Investig Dermatol Symp Proc 2000 Dec 5:55-60) cathelicidins, defensins, LL-37, hCAP18 (protein), β defensins , α defensins (Dig Dis Sci 2002 Jun 47:1349-55), hepcidins (Eur J Biochem 2002 Apr 269:2232-7), ubiquicidin (UBI) (J Nucl Med 2001 May 42:788-94), human lactoferrin (hLF), lysozyme, lactoferrin, secretory phospholipase A(2) (sPA(2)), matrilysin (MMP7), human neutrophil alpha-defensins 1-3 (HNP 1-3), human beta-defensin 1 (HBD-1), and human beta-defensin 2 (HBD-2) ,heparin binding protein (CAP37), human cationic antimicrobial protein (LL37), human alpha-defensin 5 (HD5), human alpha-defensin 6 (HD6), HBD-1, HBD-2, and human beta-defensin 3 (HBD-3) (J Pathol 2002 Nov 198:369-77), human DCD-1 (J Immunol Methods 2002 Dec 270:53), HE2alpha and HE2beta1, human HE2-gene derived transcripts, HE2beta1 (Biol Reprod 2002 Sep 67:804-13), HE2alpha C-terminal fragments, Human β defensins 1 , β defensins 2, β defensins 3, β defensins 4, HD-5, HD-6, homolog HtpG, Bactericidal/permeability-increasing protein [BPI] (Mol Microbiol 1995 Aug 17:523-31), Dermicidin (Nat Immunol 2001 Dec 2:1133-7),
histone H2B (Eur J Biochem 1996 Apr 1;237(1):86-92), alpha-**Melanocyte stimulating hormone** (Neuroimmunomodulation-2002-2003;10(4):208-16), **antileukoprotease** (Am J Respir Crit Care Med 1999 Jul;160(1):283-90), **apolipoprotein E2** (Brain Res 1997 Feb

21;749(1):135-8, Biochemistry 2002 Oct 1;41(39):11820-3, Eur J Clin Chem Clin Biochem 1997 Aug;35(8):581-9) **apolipoproteins E, C2, and C3** (Hypertens Pregnancy 2002;21(3):199-204), **bactericidal/permeability-increasing protein (BPI) of human neutrophils** (J Biol Chem 1987 Nov 5;262(31):14891-4), **buforin** (Arch Biochem Biophys 2001 Aug 1;392(1):3-7), **CAP37** (J Clin Invest 1990 May;85(5):1468-76), **CCL28** (J Biol Chem 2000 Jul 21;275(29):22313-23), **Chromogranin A (CGA) and chromogranin B (CGB)** (Blood 2002 Jul 15;100(2):553-9), **Cystatin superfamily** (Biol Chem Hoppe Seyler 1988 May;369 Suppl:191-7), **Dermcidin** (Nat Immunol 2001 Dec;2(12):1133-7), **eosinophil cationic protein** (J Exp Med 1989 Jul 1;170(1):163-76), **ESC42** (Endocrinology 2001 Oct;142(10):4529-39), **FALL-39** (Proc Natl Acad Sci U S A 1995 Jul 18;92(15):7085-9), **HE2** (Biol Reprod 2002 Sep 67:804-13), **histatin** (Antimicrob Agents Chemother 2001 Dec 45:3437-44), **HMG-17** (J Biol Chem 1986 Jun 5;261(16):7479-84), **human cathepsin G** (BMC Dermatol 2002 Aug 30;2(1):12), **human lysosomal cathepsin G** (Curr Pharm Des 2002;8(9):695-702, J Biol Chem 1991 Jan 5;266(1):112-6), **IP-10** (J Immunol 2001 Jul 15;167(2):623-7, J Interferon Cytokine Res 2002 Dec;22(12):1175-9), **Lactoferrin** (J Mammary Gland Biol Neoplasia 1996 Jul;1(3):285-95), **lysozyme** (Anat Embryol (Berl) 2002 Jul;205(4):315-23), **antibacterial and opioid peptides** (J Neuroimmunol 2000 Sep 22;109(2):228-35), **Retrocyclin** (Proc Natl Acad Sci U S A 2002 Feb 19;99(4):1813-8), **Technetium** (Eur J Nucl Med 2000 Mar;27(3):292-301), thymosin beta-4 (Eur J Biochem 1996 Apr 1;237(1):86-92), **Adrenomedullin,** (J Biol Chem 1998 Jul 3;273(27):16730-8), **Tryptase and Chymase and mast cell granule serine proteinases** (Immunology 2002 Apr;105(4):375-90), **elafin** (SKALP) J Invest Dermatol 2002 Jul;119(1):50-5,

recently discovered:
angiogenin 4 (Ang4)- Hooper LV, Stappenbeck TS, Hong CV, Gordon JI. Angiogenins: A new class of microbicidal proteins involved in innate immunity. Nature Immunology, March 2003, **Human LAK cells antimicrobial peptides** (Hua Xi Yi Ke Da Xue Xue Bao 2002 Jan;33(1):87-90)

Bioinformatics approach:

28 potential candidates for defensin like peptides were computationally discovered: Proc Natl Acad Sci U S A 2002 Feb 19;99(4):2129-33, Schutte BC, Mitros JP, Bartlett JA, et al.

Algae in industrial production of antibodies

Algae are used to industrially mass-produce the antibody.

APPLICATION METHODS

Local injection in saline solution in cases of for example arthritis.
Topical application in lipid or saline solution or in cream on the skin of psoriasis legion.
Inhaler in solution in Cystic fibrosis and for asthma.

Cream solutions can include any lipids or organic alcohols or chemicals including for example benzyl alcohol, macrogol, hexylene glycol, carbomer, ascorbic acid, butyl hydroxyainisole, butyl hydroxytoluene, disodium edentate, water, trometamol, poxoamer.

AUTOIMMUNE DISEASED THAT ARE TRIGGERED BY ANTIMICROBIAL PEPTIDES

a. crohn's disease (inflammatory bowel diseases)
b. psoriasis
c. dermatitis
d. arthritis and rheumatoid arthritis
e. atherosclerosis
f. asthma
g. cystic fibrosis
h. multiple sclerosis
i. diabetes
j. lupus
k. scleroderma
l. thyroid inflammatory diseases
m.celiac disease
n. fatigue syndromes
o. eating disorders
p. graves disease
q. reiters syndrome
r. myasthenia gravis
s. dermatomyosis
t. addison's disease
u. pernicious anemia
v. Guillain-Barre' syndrome
w. fibromyalgia
x. goodspature
y. atopic allergy
z. celiac, Alzheimer, Influenzae and respiratory disease, Iron deficiency anemia and Anemia of inflammation, Atopic dermatitis, Cholesteatoma, chronic autoimmune gastritis
ag. Active Chronic Hepatitis, Dermatomyositis, Dermatomyositis, Hashimoto's Thyroiditis, Lymphopenia (some cases), Pemphigoid, Phacogenic Uveitis, Primary Biliary Cirrhosis, Raynauds, Sjogren's Syndrome, Takayasu's Arteritis, Type B Insulin Resistance, Autoimmune Atrophic Gastritis, (Type I) Diabetes, Goodpasture's Syndrome, Idiopathic Adrenal Atrophy, Lambert-Eaton Syndrome, Mixed Connective Tissue Disease, Pemphigus Vulgaris, Polyarteritis Nodosa, Primary Sclerosing Cholangitis, Reiter's Syndrome, Schmidt's Syndrome, Sympathetic Ophthalmia, Temporal Arteritis, Ulcerative Colitis, Anti-phospholipid Syndrome, Achlorhydra Autoimmune, Cushings Syndrome, Discoid Lupus, Grave's Disease, Idiopathic Thrombocytopenia, Lupoid Hepatitis, Pernicious Anema,

Polyglandular Auto. Syndromes, Relapsing Polychondritis, Scleroderma – CREST, Systemic Lupus Erythematosis, Thyrotoxicosis, Wegener's Granulomatosis
All other autoimmune diseases listed in medical dictionaries as "autoimmune diseases" and that are triggered by antimicrobial peptides.

CLAIMS:
What is claimed:

1. A method for treating and preventing disease to human and mammalian species.

2. a method in claim 1 in which the disease is an inflammation or autoimmune diseases or other disease causing abnormal growth or differentiation

3. a method in claim 2 in which the procedure uses blocking agents in order to treat and to inhibit the cause of inflammation and its pathways

4. the method in claim 3 in which the blocking agent is a monoclonal antibody, antibody fragment, mixture or derivative thereof, antagonist, antisense, chemical inhibitors, or mimics that bind to peptides, receptors, polymorphic peptides, polypeptides, neutrophili, derived from the patient, antimicrobial peptides, and proteins of diseases patient (including those expressing polymorphism) and inhibits their activity

5. a monoclonal antibody, antibody fragment, mixture or derivative thereof, antagonist, or a mimic which binds to peptides and inhibits its activity and which is produced by the method in claim 4

6. a cell which expresses a monoclonal antibody, antibody fragment, mixture or derivative thereof of type as in claim 5.

7. a cell as claimed in claim 6, which is from a hybridoma cell line

8. a hybridoma according to claim 7, wherein the hybridoma is a mouse hybridoma

9. a pharmaceutical preparation comprising a monoclonal antibody, antibody fragment, mixture or derivative thereof as claimed in claim 3

10. compositions for treating autoimmunity in a patient undergoing therapy comprising a monoclonal antibody, antibody fragment, mixture or derivative thereof as claimed in claim 5

11. a method for screening for the blocking monoclonal antibodies in claim 5 so as to inhibit inflammation or inflammatory or autoimmune disease

12. the method in claim 11 using survival rates in cultures of microbes or bacteria with the antimicrobial peptides and the antibodies or antagonists in claim 5.

13. a method for testing and screening the effectiveness of the antibody or antagonist in claim 5 on psoriasis lesions and lesions of other diseases included in claim 20, Psoriasis animal models, humans, human biopsies of normal or pathological involved lesion maintained in an organotypic culture containing plasma and lymphocytes of patients suffering from the disease having and not having polymorphism on antimicrobial peptides or their genes and promoters.

14. the method in claim 13 using Quantitative Evaluation of Epidermal Thickness, cell count or histological evaluation

15. the method in claim 14 using statistical analysis and ANOVA.

16. A method in claim 4 that uses small interference RNA's as down regulators of peptide production

17. A method in claim 4 where the antibody has been transposed by fusion method of chimerics- attaching the Fc portion of the antibody to a human Fc portion of antibody peptide.

18. A method of industrial production of the antibody using algae and transfected algae

19. An antagonist in claim 4 that is an analogue of the antimicrobial peptide

20. An autoimmune disease in claim 2 that includes amongst others the following diseases:

a. crohn's disease (inflammatory bowel diseases)
b. psoriasis
c. dermatitis
d. arthritis and rheumatoid arthritis
e. atherosclerosis
f. asthma
g. cystic fibrosis
h. multiple sclerosis
i. diabetes
j. lupus
k. sclerodema
l. thyroid inflammatory diseases
m. celiac disease
n. fatigue syndromes
o. eating disorders
p. graves disease
q. reiters syndrome
r. myasthenia gravis
s. dermatomyosis
t. adison's disease
u. pernicious anemia
v. guillen bar
w. fibromyalgia
x. goodspature
y. atopic allergy
z. celiac, Alzheimer, Influenzae and respiratory disease, Iron deficiency anemia and Anemia of inflammation, Atopic dermatitis, Cholesteatoma, chronic autoimmune gastritis
ag. Active Chronic Hepatitis, Dermatomyositis, Dermatomyositis, Hashimoto's Thyroiditis, Lymphopenia (some cases), Pemphigoid, Phacogenic Uveitis, Primary Biliary Cirrhosis, Raynauds, Sjogren's Syndrome, Takayasu's Arteritis, Type B Insulin Resistance, Autoimmune Atrophic Gastritis, (Type I) Diabetes, Goodpasture's Syndrome, Idiopathic Adrenal Atrophy, Lambert-Eaton Syndrome, Mixed Connective Tissue Disease, Pemphigus Vulgaris, Polyarteritis Nodosa, Primary Sclerosing Cholangitis, Reiter's Syndrome, Schmidt's Syndrome, Sympathetic Ophthalmia, Temporal Arteritis, Ulcerative Colitis, Anti-phospholipid Syndrome, Achlorhydra Autoimmune, Cushings Syndrome, Discoid Lupus, Grave's Disease, Idiopathic Thrombocytopenia, Lupoid Hepatitis, Pernicious Anema, Polyglandular Auto. Syndromes, Relapsing Polychondritis, Scleroderma – CREST, Systemic

Lupus Erythematosis, Thyrotoxicosis, Wegener's Granulomatosis, Diffuse panbronchiolitis.
All other autoimmune diseases listed in medical dictionaries as "autoimmune diseases" and that are triggered by antimicrobial peptides.
Za. Cancer, tumors, skin carcinoma, leukemia.

21. an antimicrobial peptide referred to in claim 4 that is one or any combination of the following:

a. cathelicidins
b. defensins
c. LL-37
d. hCAP18 (protein)
e. defensins
f. α defensins
g. hepcidins
h. ubiquicidin (UBI)
i. human lactoferrin (hLF)
j. human DCD-1
k. HE2alpha and HE2beta1
l. human HE2-gene derived transcripts
m. HE2beta1
n. and HE2alpha C-terminal fragments
o, Human defensins 1., defensins 2, defensins 3, defensins 4, HD-5, HD-6
p. eNAP-1, HtpG
q. lactoferrin
r. histones, H2A, H2B
s. dermicidin
t:- Alpha-defensins, beta-defensins 1 to 6, Science 2002 Nov 298:995-1000 histones H2A and H2B (J Immunol 2002 Mar 168:2356-64), glycosaminoglycans (J Investig Dermatol Symp Proc 2000 Dec 5:55-60) cathelicidins, defensins, LL-37, hCAP18 (protein), β defensins , α defensins (Dig Dis Sci 2002 Jun 47:1349-55), hepcidins (Eur J Biochem 2002 Apr 269:2232-7), ubiquicidin (UBI) (J Nucl Med 2001 May 42:788-94), human lactoferrin (hLF), lysozyme, lactoferrin, secretory phospholipase A(2) (sPA(2)), matrilysin (MMP7), human neutrophil alpha-defensins 1-3 (HNP 1-3), human beta-defensin 1 (HBD-1), and human beta-defensin 2 (HBD-2) ,heparin binding protein (CAP37), human cationic antimicrobial protein (LL37), human alpha-defensin 5 (HD5), human alpha-defensin 6 (HD6), HBD-1, HBD-2, and human beta-defensin 3 (HBD-3) (J Pathol 2002 Nov 198:369-77), human DCD-1 (J Immunol Methods 2002 Dec 270:53), HE2alpha and HE2beta1, human HE2-gene derived transcripts, HE2beta1 (Biol Reprod 2002 Sep 67:804-13), HE2alpha C-terminal fragments, Human β defensins 1 , β defensins 2, β defensins 3, β defensins 4, HD-5, HD-6, homolog HtpG, Bactericidal/permeability-increasing protein [BPI] (Mol Microbiol 1995 Aug 17:523-31), Dermicidin (Nat Immunol 2001 Dec 2:1133-7),
histone H2B (Eur J Biochem 1996 Apr 1;237(1):86-92), alpha-**Melanocyte stimulating hormone** (Neuroimmunomodulation-2002-2003;10(4):208-16), **antileukoprotease** (Am J Respir Crit Care Med 1999 Jul;160(1):283-90), **apolipoprotein E2** (Brain Res 1997 Feb 21;749(1):135-8, Biochemistry 2002 Oct 1;41(39):11820-3, Eur J Clin Chem Clin Biochem 1997 Aug;35(8):581-9) **apolipoproteins E, C2, and C3** (Hypertens Pregnancy 2002;21(3):199-204), **bactericidal/permeability-increasing protein (BPI) of human neutrophils** (J Biol Chem 1987 Nov 5;262(31):14891-4), **buforin** (Arch Biochem Biophys 2001 Aug 1;392(1):3-7), **CAP37** (J Clin Invest 1990 May;85(5):1468-76), **CCL28** (J Biol

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recently discovered:

angiogenin 4 (Ang4)- Hooper LV, Stappenbeck TS, Hong CV, Gordon JI. Angiogenins: A new class of microbicidal proteins involved in innate immunity. Nature Immunology, March 2003, **Human LAK cells antimicrobial peptides** (Hua Xi Yi Ke Da Xue Xue Bao 2002 Jan;33(1):87-90)

50. Ashcroft GS, Lei K, Jin W, Longenecker G, Kulkarni AB, Greenwell-Wild T, et al. Secretory leukocyte protease inhibitor mediates non-redundant functions necessary for normal wound healing. Nat Med 2000;6:1147-53. 7

Table 1
Chemokine receptors, expression pattern, ligands and involvement in disease

Receptors	Ligands	Receptor-expressing cells	Diseases
CCR1	CCL3, CCL5, CCL7, CCL8, CCL13, CCL14, CCL15, CCL23	monocyte, dendritic cell (immature), T cell, neutrophil, eosinophil, mesangial cell, platelet	MS, RA, transplant, asthma, nephritis
CCR2	CCL2, CCL7, CCL8, CCL13	monocyte, dendritic cell (immature), T cell, basophil, natural killer cell, fibroblast, endothelial cell	MS, RA, transplant, asthma, atherosclerosis
CCR3	CCL5, CCL7, CCL8, CCL11, CCL13, CCL14, CCL15, CCL24, CCL26	eosinophil, basophil, mast cell, T cell (Th2), platelets, airway epithelial cell	asthma, atopic dermatitis
CCR4	CCL17, CCL22	dendritic cell, basophil, T cell (Th2, Treg, skin-homing), platelets	asthma, atopic dermatitis
CCR5	CCL3, CCL4, CCL5, CCL8,CCL11, CCL13, CCL14	T cell (Th1), dendritic cell, monocyte, natural killer cell	MS, RA, transplant, nephritis, IBD, AIDS
CCR6	CCL20	dendritic cell (immature), T cell, B cell	psoriasis
CCR7	CCL19, CCL21	dendritic cell (mature), T cell, B cell, natural killer cell	transplant
CCR8	CCL1, CCL16	T cell (Th2, Treg), monocyte, natural killer cell, B cell, endothelial cell	Asthma
CCR9	CCL25	T cell (gut-homing)	IBD
CCR10	CCL27, CCL28	T cell (skin-homing), melanocyte, Langerhans cell, dermal endothelium, dermal fibroblast	Psoriasis, Atopic dermatitis
CCR11	CCL19, CCL21, CCL25	astrocyte	
CXCR1	CXCL5, CXCL6, CXCL8	neutrophil, monocyte, endothelial cell, astrocyte	sepsis, atherosclerosis, COPD, psoriasis
CXCR2	CXCL1, CXCL2, CXCL3, CXCL5, CXCL7, CXCL8	neutrophil, monocyte, eosinophil, endothelial cell	sepsis, atherosclerosis, COPD, psoriasis
CXCR3	CXCL9, CXCL10, CXCL11	T cell (Th1), B cell, mesangial cell, smooth muscle cell, microglia	MS, RA, transplant, sarcoidosis, COPD
CXCR4	CXCL12	T cell, dendritic cell, monocyte, B cell, neutrophil, platelet, astrocyte	AIDS, cancer
CXCR5	CXCL13	B cell, T cell (T_{FH}), astrocyte	cancer
CXCR6	CXCL16	T cell (Th1)	RA
XCR1	XCL1, XCL2	T cell	
CX_3CR1	CX_3CL1	T cell (Th1), natural killer cell, astrocyte	RA, atherosclerosis

Th, T helper cell; T_{FH}, T follicular helper cell; Treg, regulatory T cell; MS, multiple sclerosis; RA, rheumatoid arthritis; COPD, chronic obstructive pulmonary disease.

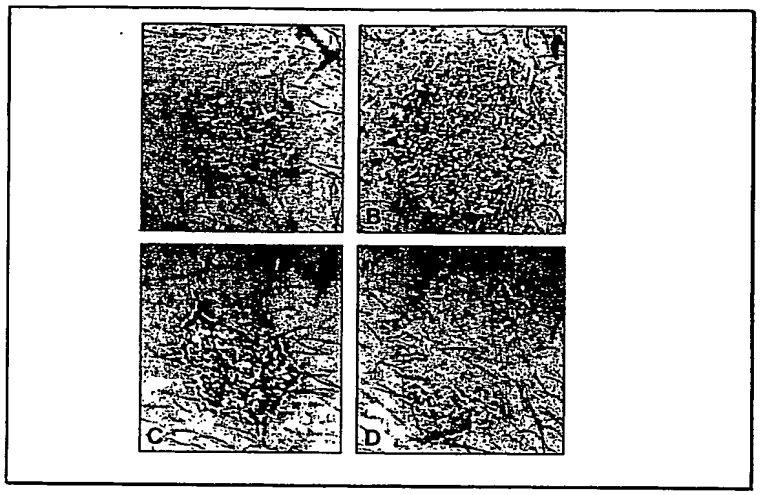
HUMAN TRIALS

Human Trials were carried out.
For Psoriasis and dandruff the results indicated positive results with no noticeable side effects.

Using topical application of antibodies to defensin and LL-37, hyper proliferation in psoriasis was halted.

The following photographs indicating improvement in psoriasis are shown.

Compared to the control, a significant decrease in proliferation in the treated legion was noticed by a blind trial after a period of 8 hours. Improvement continued with a significant decrease in inflammation and proliferation within three days.



A: Control Day 0
B: Applied Lesion Day 0

C: Control Day 3
D: Applied Lesion Day 3

Application method: Topically using a wet watman paper. Antibody dilution in 0.1% BSA/PBS.